

Learning from History: Strengthening the Design of AD/ADRD Pragmatic Clinical Trials

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Executive Summary

On April 3, 2023, the Board on Health Care Services (BHCS) of the National Academies of Sciences, Engineering, and Medicine convened an expert panel on the design of pragmatic clinical trials (PCTs) for the study of Alzheimer’s disease and related dementias (AD/ADRD). Six presenters described research priorities for improving the design of PCTs, with the goal of improving care and support for people living with dementia and their caregivers. There is a clear unmet need to better serve AD/ADRD patients and their caregivers. At least 50 percent of AD/ADRD patients are undiagnosed and at least 10 percent of elderly patients experience abuse.

Presenters emphasized six main research priorities: maintaining the fidelity of PCTs, harnessing caregiver engagement through patient portals, promoting the development and utilization of care teams, considering the risk of bias in PCT statistical analyses, promoting large-scale systemic change through leadership and training, and recognizing the challenges and opportunities in health disparities research. A common theme was the need to improve the design of PCTs, through improving pragmatic measures, increasing the tempo of results, recognizing the challenges presented by heterogeneous populations, and reducing the risk of bias. BHCS members found the concept of caregiver engagement with patient portals to be compelling, particularly the potential to leverage caregiver input to develop learning health systems that improve care. BHCS considered the idea of a small, funded project on patient portals to better understand their benefits.

Increasing Pragmatic Measures Aids in Improving Fidelity in PCTs

PCTs present advantages to traditional control trials for AD/ADRD research because they can test interventions in complex, real-world settings. However, conditions are less controlled and trial adherence can be low, which often leads to inconclusive results or negative trials. Systems such as PRECIS-2 are useful in measuring the pragmatic elements of PCTs. Fidelity measures define whether interventions actually reach trial participants and are key to assessing the potential success of a PCT. Researchers must make intentional choices about the level of pragmatism in their trial designs to conduct a fair test of a given intervention.

Research Opportunities

1. Improve PCT design by utilizing PRECIS-2 scoring to promote pragmatic measures.
2. Prioritize flexibility of intervention delivery as a key aspect of PRECIS-2 scoring but can undermine the likelihood of a successful PCT.

Improving AD/ADRD Care Is a Team Activity

Primary care is struggling to deliver care to AD/ADRD populations. Primary care teams should extend beyond providers by including social workers, nurses, pharmacists, case managers, community health workers, and medical assistants. Care should be delivered in the context in which patients live and work. To maximize the limited resources of current health care systems and change the paradigm of AD/ADRD care, precision health care models should target disadvantaged populations with high morbidity, limited support, and social isolation.

Research Opportunities

1. Expand models of care for AD/ADRD that extend beyond primary care providers, and create linkages with community-based organizations, in particular.
2. Include social workers in care teams to help address social determinants of health.
3. Plan innovative interventions that use limited resources to deliver preventive care to high-risk populations.

Address Ambiguities and Bias in CRT Statistical Analyses

Cluster randomized trials (CRTs) are a subset of PCTs that compare interventions within various groups to assess their potential benefits. Challenges arise in the statistical analyses of these trials because eligibility criteria are broad, intervention contexts are heterogeneous, and recruitment practices are diverse. A key question for CRT designers is how they will assess intervention effectiveness and how to precisely quantify “effectiveness.” To address potential biases and ambiguities stemming from statistical analyses, researchers should specify estimands in a transparent fashion—that is, making sense of the target inference at the *outset* of the study—rather than allow statistical methods to dictate the scientific question of interest. Two examples can lead to ambiguity in CRT statistical analyses. First, informative cluster sizes can lead to different definitions of treatment effect that correspond to different scientific questions of interest. Second, selection bias can occur post-randomization in studies that are not blinded and where recruitment happens after randomized assignment.

Research Opportunities

1. Develop methods and guidance to systematically specify estimands in ePCTs, especially CRTs.
2. Develop methods and guidance to address post-randomization selection bias and generalizability of results in ePCTs.
3. Develop methods to study mediation and moderation of effects in ePCTs. These issues also closely relate to estimands and estimand-aligned inference.

Produce Systemic Change Through Leadership and Training

PCTs can be vehicles for systemic change in improving care in elderly populations by enabling local teams to innovate and empowering leadership to promote stakeholder participation. All relevant stakeholders must be considered and involved as appropriate. The social nature of systemic change cannot be understated; early adopters grant credibility to large-scale studies and enhance fidelity. However, enabling quality improvement programs (by providing resources, for example) is much more difficult than delivering them in the real world. Recruiting leadership and assessing site readiness are key to improving outcomes. Ensuring participants have enough time and support to deliver a pragmatic intervention is also key. Stepped-wedge trial designs can be useful in these types of PCTs, but should be carefully planned to avoid hampering the performance of sites that activate later in the trial or contamination from knowledge of the intervention spreading to clusters that will be activated later.

Research Opportunities

1. Promote the social aspects of systemic change by enabling local learning, stakeholder engagement, and recruitment of local leadership to champion interventions.

2. Investigate sources of potential bias in stepped-wedge trial design.
3. Use collaborative models and quality improvements that employ iterative learning processes.
4. Ensure teams that will deliver the intervention have enough time and support to be effective in a pragmatic setting.

Incorporate Diversity, Equity, and Inclusion Principles into PCT Design

Differences in treatment for minority communities can result in delayed interventions and poor health outcomes. Minority groups can provide insight into how intersections of social, behavioral, and physical conditions impact interventions. Research is needed on the explanatory mechanisms that underly health disparities. The biobehavioral origins of health disparities must be investigated. Tailoring effective interventions for minority populations requires nuanced understanding of the physical and cultural barriers to care. Engaging families in minority populations is an effective recruitment strategy, and recruiters should prioritize transparency and offer study insights to build trust.

Research Opportunities

1. Consider oversampling minority populations to study causal pathways in health and disease across racial and ethnic groups.
2. Carefully design recruitment of minority populations to promote transparency and communicate the value of study-derived insights that can be delivered back to communities.
3. Investigate preferred communication styles prior to recruiting from minoritized populations.

Meeting Summary

Opening Remarks from the National Institute on Aging

Theresa Kim, Ph.D., NIA, Program Officer, Division of Behavioral and Social Research

The National Institute on Aging (NIA) is one of 27 Institutes and Centers at the National Institutes of Health (NIH). NIA's mission is to support research to better understand the nature of aging and extend healthy and active years of life. The Division of Behavioral and Social Research (BSR) is one of four extramural divisions within NIA, which focuses specifically on social, behavioral, and economic research infrastructure and training regarding the process of aging at the individual and societal levels. BSR is divided into two branches: Population and Social Processes and Individual Behavioral Processes. The former focuses on demographic, institutional, and other factors—including health systems, Medicare, Medicaid, and nationally represented longitudinal studies. The latter Branch focuses on psychosocial, behavioral, and interpersonal processes and interventions at the individual and dyadic levels.

BSR relies on experts, including those at the Board on Health Care Services (BHCS) of the National Academies of Sciences, Engineering, and Medicine (NASEM) to identify gaps and opportunities in key areas of research. The NIA National Advisory Council on Aging (NACA) recommends new directions for NIA research every 5 years. In 2019, NACA called for increasing the diversity of participants in AD/ADRD studies, incorporating a focus on mediators and moderators to help identify how interventions may work, and considering subgroup analyses for heterogeneity in treatment. NACA also promoted research on behavior change in individuals and support for organizations that could implement interventions.

Primary Care for People Living with Dementia

Medicare mandates annual wellness visits, which are typically covered by the Affordable Care Act. The U.S. Preventative Services Taskforce (USPSTF) does *not* recommend screening for Alzheimer's disease and related dementias (AD/ADRD), citing insufficient understanding of the benefits and harms of screening. However, NIA does support research into opportunities in primary care to facilitate screening of elderly patients for advanced care planning, elder abuse, and medication management.

Elder abuse is often underreported. Barriers to elder abuse screening include overly busy primary care providers and patients' fear of stigma. A 2021 CMS report estimated a 10 percent prevalence rate of abuse in Medicare patients over 70 years old. Evidence also suggests the need for new avenues of care in elderly populations. In 2010, the Centers for Medicare & Medicaid Services (CMS) reported that 69 percent of Medicare patients had two or more chronic conditions that required medication management.

AHRQ Report on the Limitations of PCTs and RCTs

The Agency for Healthcare Research and Quality's (AHRQ) recently released a report on pragmatic clinical trials (PCTs) and randomized clinical trials (RCTs), which offer the potential to

innovate the delivery of primary care for aging patients and persons living with dementia (PLWD)—but with notable limitations. AHRQ cited lower than average subject retention due to illness and mortality, underpowered studies due to small sample sizes, and a high risk of selection, attrition, and fidelity biases. Lack of diversity in U.S.-based studies also remains a challenge. Further, AHRQ noted that PCTs and RCTs are not using the NIH Stage Model, which encourages examination of the mechanisms of behavior change at every stage of intervention development to increase the success of intervention implementation.

Meeting Objectives

The objectives of this meeting were to discuss (1) how primary care can improve pragmatic clinical studies related to AD/ADRD diagnoses and (2) how to generate evidence regarding best practices in routine care for PLWD. Participants were encouraged to examine limitations of existing PCTs and RCTs in AD/ADRD research, including:

- Bias and inadequate power,
- Inefficient application of the NIH Stage Model, and
- Difficulties in scaling up interventions.

This meeting aims to foster discussion on the best methods to conduct PCTs in AD/ADRD research and to examine the role of primary care in the screening of elder abuse, medication, management, and advanced care planning.

Discussion

Elder abuse is both underreported and understudied. Primary care providers can help with screening by normalizing conversations on this topic, but they need additional guidance. A recent trans-NIH workshop on elder and child abuse revealed some insights. Prevention models can prompt primary care providers to look for stressors, such as lack of resources and overworked caregivers, and act before problems become acute. However, a lack of provider training and inconsistencies in various state regulations present challenges for developing prevention models.

The most critical aspect of primary care for improving aging patients' outcomes is the team surrounding the provider, which may include social workers and community organizations. A recent [study](#) showed that providers would need a 26-hour workday to meet the current guidelines regarding adequate care. Moreover, the social workforce in hospitals has been reduced, and positions in primary care remain unfilled, a situation that the COVID-19 pandemic has exacerbated. A broad commitment to rebuilding primary infrastructure is needed to improve primary care for aging patients and PLWD, and to support their caregivers.

Evidence for Dementia Care: Tradeoffs Between What We Need and What We Want

David Reuben, M.D, Chief, UCLA Center for Health Sciences Division of Geriatrics

Policymakers require evidence to inform their decisions, which can be separated into four categories: RCTs, PCTs, quasi-experimental studies, and expert opinion (e.g., based on case studies). Each of these categories has specific strengths: RCTs are universally respected; PCTs simulate real-world conditions; quasi-experimental studies do not require randomization and may not require consent; and expert opinion provides for rapid data acquisition. Nevertheless, these four categories also have significant weaknesses. RCTs are lengthy, expensive, and difficult to generalize. PCTs are also often lengthy and expensive—and risk a lack of rigor in data collection and measurement of outcomes. In quasi-experimental studies, intervention and control groups may have baseline imbalances, which confound results, whereas expert opinions lack a control group.

Comparing Traditional and Pragmatic Trials

Traditional explanatory trials (i.e., RCTs) confirm physiological or clinical hypotheses; by contrast, PCTs inform clinical or policy decisions by providing evidence for interventions in real-world clinical practice.

RCTs test interventions against controls using rigid protocols and minimal variation to determine cause and effect. Participants are well-defined and carefully selected. Measures used in RCTs may require data collection outside routine clinical care, and results may not be relevant to everyday practice.

By contrast, PCTs test real-world treatments using flexible protocols and customize local practices with the goal of improving practice and implementing new, more effective clinical or policy decisions. PCT participants are more representative of the general population, and eligibility is typically less strict than for RCTs. In PCTs, measures are collected in clinical settings, and results are intended to be relevant to everyday practice.

The Pragmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2) wheel assesses the level of pragmatism in PCTs by providing scores for eligibility, recruitment, setting, organization, flexibility of delivery, flexibility of adherence, follow-up, primary outcome, and primary analysis. PCTs require a significant amount of stakeholder input, the participation of diverse representative populations, and the availability of multiple heterogeneous settings. The outcomes of PCTs need to be relevant to care and policy decisions in real-world settings and consistent with preexisting clinical workflows. All these aspects help communicate a significant return on investment for health systems.

D-CARE Trial

The Patient-Centered Outcomes Research Institute (PCORI) and NIA funded a PCT to compare the effectiveness and cost-effectiveness of community-based and health system-based

dementia care and to compare both to usual care. D-CARE recruited participants at four clinical trial sites and enrolled a total of 1,000 participants in each intervention arm and 150 participants in a control group. Inclusion criteria were living in community settings (not nursing home or hospice), a dementia diagnosis, a caregiver that spoke English or Spanish, and a partnering physician engaged with the trial. Patients were recruited using the EPIC electronic health record (EHR) system to generate lists of PLWD and through referrals from providers, patients, caregivers, and sites.

The design of the health systems intervention arm was based on the University of California, Los Angeles (UCLA) care model, and care was provided by advanced practice provider (nurse practitioners or physicians assistants) Dementia Care Specialists. In the community-based arm, based on the Benjamin Rose Institute model, dementia care was provided by social workers or nurse Care Consultants. The controls were given the telephone number of the Alzheimer's Association helpline. The primary outcomes for PLWD and their caregivers are reduction of severity in behavioral symptoms of the person living with dementia and caregiver strain indices. Secondary outcomes measures include caregiver distress resulting from patient behavioral symptoms, caregiver depression, and caregiver self-efficacy. Tertiary outcomes include many utilization outcomes, such as days spent at home.

PRECIS-2 scoring was applied to D-CARE to assess the level of pragmatism in this PCT. The overall score was 3.7 (with 5 being the highest possible score). D-CARE scored high in eligibility, setting, and organization—and scored highest on the primary outcome and primary analysis. Lower scores were given for recruitment, flexibility, and follow-up. Flexibility in delivering care is a key PRECIS-2 score but may compromise fidelity (i.e., ensuring an intervention is actually delivered) and quality of care. Even with the onset of the pandemic at trial launch, adherence to receiving the initial intervention was above 90 percent in both arms. Follow-up for patient participants in D-CARE is ongoing. Results will likely be published in 2024.

Conclusions

PCTs have some advantages over RCTs for AD/ADRD research. For example, PCTs can more easily incorporate participants with multiple chronic conditions in treatment regimens that are more applicable to real-world settings. However, PCTs also have notable disadvantages: fidelity is difficult to maintain, and EHR data may be insufficient to inform analyses. Ultimately, PCTs cannot be perfectly pragmatic. Researchers involved in trial designs must make choices to develop a fair test of an intervention. Policymakers should weigh all available data and consider the strength and generalizability of the evidence, as well as the practicality of tested interventions.

Discussion

Fidelity is essential to the success of PCTs; however, adherence to study regimens within PCTs can be challenging because real-world settings can be unpredictable. For example, in a recent [PCT](#) involving a video-based intervention for nursing home residents, only 22 percent of eligible residents received a simple intervention. D-CARE addressed fidelity by allowing each of the two

intervention groups to create and monitor fidelity measures within their trial arms. In the health system arm of D-CARE, communication between providers and inpatient teams was critical to maintaining intervention fidelity when patients were hospitalized. Participant charts were also de-identified and reviewed for any fidelity issues so that additional provider training could be implemented, if necessary. In the community-based care arm, practitioners used nearly two dozen measures to monitor fidelity of care.

Catalyzing Dementia Care Research in Real-World Care Delivery

Jennifer Wolff, Ph.D., Director, Johns Hopkins University Center for Integrated Care

Learning Health Systems (LHSs) have the potential to create rapid, cyclical improvements in dementia care. The support and engagement of caregivers is critical to the success of LHSs. LHSs are defined as “science, informatics, incentives, and culture that are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process, patients and families as active participants in all elements, and new knowledge captured as an integral byproduct of the delivery experience.” The science of dementia care is strong, but the means of measuring the impact of interventions is weak—which necessitates LHSs to address system-level gaps, including the following:

- Half of dementia patients are undiagnosed.
- Racial and ethnic disparities in dementia treatment and care persist.
- Caregivers are not routinely identified, and their support needs go unmet.
- Health care providers experience high levels of burnout.

In a 2020 study commissioned by NIA, AHRQ reviewed more than 8,000 studies, including 850 RCTs, and concluded that little evidence supports the widespread dissemination of any general care approaches for PLWD.

PCTs provide opportunities to address contextual barriers, as well as information on how to reach target populations, prepare the workforce, and align interventions with reimbursement mechanisms. However, PCTs are frequently unable to discern mechanisms of action and face design challenges. Implementation and treatment effects may be highly contextual—particularly when more than one program may be needed to address the complex needs of AD/ADRD patients.

Dementia Learning Health Systems

Our understanding of dementia prevalence, inequities, and care experiences relies on curated data collected in national surveys and population-based datasets—which are disconnected from systems that typically diagnose dementia patients. LHSs in dementia care have the potential to address softer priorities (such as clinician burnout), accelerate the pace of innovation, and address informatics challenges inherent in executing large-scale PCTs. Systems-level challenges in AD/ADRD care also require additional data on underserved populations and the dissemination of comprehensive care models.

The fragmentation of costs makes AD/ADRD a model condition for health systems to focus on to improve quality. LHSs can help identify various aspects of health systems that need improvement, for example, reimbursement codes to diagnose dementia. The NIH Stage Model is intended to help improve the efficiency of health systems, but longstanding gaps remain between investigation and implementation of various interventions.

Health systems can draw upon caregiver experiences to implement LHSs and improve care. Caregivers and the families of PLWDs are at the forefront of dementia care. Supporting these individuals and learning from their experiences can improve treatment and its impact. Support of caregivers should be part of industry best practices, and dementia planning codes in EHR systems that account for caregiver involvement in AD/ADRD care are an essential element of care quality measurement. Economic modeling shows that scaling caregiver support leads to large cost savings for public and private stakeholders.

Leveraging Patient Portals

The invisibility of caregivers presents a major methodological challenge to improving caregiver support. Caregivers typically operate outside of financial, health care, and regulatory frameworks. Data on caregivers is not systematically captured. Patient portals can help improve care and support for caregivers by giving caregivers proxy access with unique credentials. This proxy access allows health systems to identify caregivers and provide targeted outreach.

Research is limited on caregiver use of patient portals. A recent [scoping review](#) found that caregiver proxy access is low. However, analyses of portal messages and caregiver surveys show that caregiver portal use is quite high. Up to 60 percent of patients accessed patient portals with caregiver help, and shared access was common in populations who needed additional support in navigating health systems. The review also showed that two-thirds of message threads were authored by caregivers and 95 percent signed in with patient credentials. Moreover, PLWDs were three times as likely to have a care proxy in a patient portal, but this number only accounts for 10.4 percent of this group of patients.

Systematic engagement of caregivers in an LHS and patient portal shows significant promise for improving care for PLWD and support for caregivers. Caregivers can help providers better tailor treatments and support for PLWDs. Patient portals can help disseminate tools and resources to caregivers, including behavioral care safety tips and legal and financial planning. Health system administrators can also employ machine learning to conduct risk assessments and flag patient/caregiver dyads in need of intervention.

Discussion

The ability to grant proxy access for caregivers into the EPIC system is fairly new and may not be universally understood. Several EHR vendors now allow proxy access, and new studies on uptake of shared access are needed. BHCS may consider a small-funded project on patient portals to better understand their benefits. NIA funding mechanisms could also foster pilot programs to build LHSs using patient portals.

Patient portals also present a few significant challenges. Some portal systems introduce barriers to messaging, such as poor user interfaces and character limits. Providers also struggle to respond to the volume of messages. Broadening the group of providers and other members of the care team (such as social workers) who can respond could help relieve this burden. Privacy is also a significant concern for vulnerable PLWD populations, and proxy access to patient portals poses complex ethical issues regarding the potential for abuse.

Reengineering Care to Meet the Needs of Persons Living with Dementia and Their Care Partners Residing in the Community

Ab Brody, Ph.D. Director, NYU Hartford Institute for Geriatric Nursing

The NIA-funded Imbedded Pragmatic Alzheimer's disease (AD) and AD-Related Dementias (AD/ADRD) Clinical Trials (IMPACT) Collaboratory has done extensive work in PCTs for aging participants and PLWD. The IMPACT Collaboratory has funded 17 pilot projects and 4 demonstration projects—as well as several PCTs. The experience of the IMPACT Collaboratory could provide insights into conducting PCTs in this population. A NASEM 2021 report on PCTs called for the following:

- Paying for primary care teams to care for people, not doctors to deliver services.
- Ensuring that high-quality primary care is available to every individual and family in every community.
- Training primary care teams where people live and work.
- Designing information technology that serves the patient, family, and interprofessional care team.
- Ensuring that high-quality primary care is implemented in the United States.

Lessons Learned from the IMPACT Collaboratory and Other Research

Only 13 percent of primary care providers are confident in their ability to diagnose dementia, which presents a significant upstream problem because a diagnosis is needed to connect patients and caregivers with resources. Minoritized groups face significant delays in diagnosis, limited provider attention and resources for caregivers, and social determinants of health (SDOH) that worsen symptoms and reduce access. Primary care providers often intervene to treat behavioral and psychological symptoms long after potential preventative care could be delivered. Delayed interventions result in prescribing of antipsychotic medications, which treat behavioral problems but worsen health outcomes.

Two potential routes to improving care are worth exploring. The first is a less pragmatic approach in which policymakers “blow up the system” and develop models that are not currently viable but could become so with changes to reimbursement. The second and more pragmatic approach employs existing infrastructure and underutilized payment models to cover additional resources, including staffing and technology. The IMPACT Collaboratory has two PCTs that are exemplars of each approach. One PCT aimed to reduce antipsychotic prescription rates. It applied behavioral economics and training in a systemic, transformative approach. This

approach has the potential to improve care, but implementation is fraught. Another PCT applied an LHS using existing infrastructure. In this PCT, a machine learning system provided clinical decision support to providers for patients with high risk of mortality to prompt discussions about advanced care planning.

Care as a Team Activity

Entire primary care teams are needed to provide care for PLWD. Care teams must extend beyond the primary health care provider to include social workers, nurses, pharmacists, case managers, community health workers, and medical assistants. These teams should be integrated into communities where people live and work, and information technology should be designed to serve both interprofessional health care teams and patient caregiver networks. Primary care teams can more effectively provide for the many care needs of PLWDs—for example, by scheduling annual wellness visits, performing cognitive screening, ameliorating the effects of SDOH, addressing risk factors for cardiovascular disease, reviewing medication prescriptions, supporting care partners, and facilitating advanced care planning. Precision health care models focused on socially isolated, disadvantaged, high morbidity, and limited support populations can provide the greatest public health impact with limited health system resources. Researchers should also consider how to utilize limited revenue streams through remote monitoring, quality care incentives, and accountable care organizations.

Community health linkages can produce systems that are greater than the sum of their parts. Incorporating adult day health centers, home health services, cultural institutions, parks and recreation, advocacy organizations, and other community-based organizations into primary care can provide greater continuity of care than that provided by the current segmented health systems. PCTs, which are pragmatic and flexible, can foster team-based interventions and link community-based organizations and health systems to improve care. Technological interventions that increase communication are particularly valuable in this context, particularly infrastructure and data from previous PCTs that can be repurposed.

Discussion

Social workers are a key group for improving care to PLWD. [Studies](#) suggest that social workers can assist with advance care planning and addressing SDOH. Given the shortage of primary care providers, social workers provide critically needed supports for care teams. To facilitate the formation and functioning of care teams, EHR systems could be adapted to foster communication, build partnerships, and provide insights.

Estimand-aligned Considerations in Embedded Pragmatic Clinical Trials

Fan Li, Ph.D., Assistant Professor, Yale University School of Public Health

Cluster randomized trials (CRTs) are a subset of PCTs that analyze heterogeneous groups of patients in order to compare interventions and evaluate their effects under routine clinical practice conditions. In both CRTs and PCTs, challenges arise from the complexity of statistical

analysis and are driven by broad eligibility criteria, heterogeneity, and diverse recruitment practices. A key question for CRT trial designers to consider is their target of inference—that is, what population do the study results apply to and what is the precise formulation of the scientific question. If not addressed through careful planning and statistical analysis, results can be challenging to interpret and the target of inference can be ambiguous. Two examples of challenges are: (1) informative cluster sizes can lead to different definitions of a treatment effect and (2) post-randomization selection and recruitment can bias the intention-to-treat analysis and covariate-adjusted analysis. Discussion of these examples show that it is important that the estimand, or target of inference, should drive statistical analyses, rather than the other way around.

Example One: Informative Cluster Sizes Lead to Different Definitions of Treatment Effect

An estimand is a precise description of a treatment effect. In a CRT, the estimand includes the population, treatment conditions, endpoint, summary measures, and intercurrent events as five key attributes. Beyond these attributes, the cluster sizes in a CRT may vary; moreover, if the cluster size is associated with the outcome or treatment contrast in a cluster, then ignoring such variable cluster sizes can easily lead to ambiguity in the target of inference. In principle, two possible estimands can help researchers understand a treatment effect. The individual-average treatment effect estimand seeks to answer this question: What is the expected change in outcome associated with treatment for a typical patient? The cluster-average treatment effect estimand seeks to answer this question: What is the expected change in outcome associated with treatment for a typical provider or clinic in its natural patient panel?

Because treatment effect can differ across clusters, trial designers should think carefully about the weight that was explicitly or implicitly assigned to each cluster when an analysis method is chosen. The difference between the individual-level and cluster-level treatment effects lies in how each cluster is weighted. The former gives equal weight to each individual, while the latter gives equal weight to each cluster regardless of its size. Ongoing efforts are investigating the extent to which such informative cluster size might cause issues. These issues are summarized in one recent [study, which clarified the definition of estimands in CRTs and provided recipes for estimand-aligned analysis methods](#). Another [study](#) has shown that if statistical decisions drive estimands, biased and ambiguous treatment effect estimates in CRTs might result.

Example Two: Estimands and Post-Randomization Selection Bias

Randomization only ensures the elimination of bias before treatment assignment, not after. Selection bias can occur when participants are recruited after clusters are randomized, but recruiters and participants are not blinded. The treatment assignment can affect the recruitment process, leading to differences in intervention and control clusters. This situation commonly occurs when an intervention is perceived as beneficial. Selection bias can also occur in trials without recruitment when individuals are identified after randomization.

Recruitment processes can be affected by baseline covariates. Ambiguity in estimands can occur when the recruited sample is not representative of the overall population or when structural imbalances exist between the treatment and control groups. Careful trial design can help to avoid post-randomization selection bias, but without a careful study design and thoughtful collection of covariates, researchers cannot fully eliminate the risk of bias.

In CRTs, covariate adjustment can improve precision and account for random baseline imbalances. To develop an estimand at the beginning of a study, researchers should reflect on the scientific question and consider potential differences between the intended target population and the observed sample. The issue of bias can be illustrated under the principal stratification framework, where the strata membership is defined based on the joint potential values of the recruitment status. If the strata membership depends on unobserved covariates, adjustment for observed covariates alone cannot fully eliminate the selection bias. Innovative strategies for recruitment and thoughtful collection of baseline variables that can predict willingness to participate have potential to ameliorate statistical problems. Addressing statistical issues in trials involving AD/ADRD, which are inherently highly heterogeneous and complex, are necessary for producing meaningful analyses.

Learning about Trial Design and Implementation in a Very Messy World

Carol Peden, M.D., Executive Director, USC Center for Health System Innovation

The UK-based Enhanced Peri-Operative Care for High-risk Patients (EPOCH) study provides an example of the challenges of large PCTs in improving real-world care. The goal of this program was to improve outcomes for emergency surgery patients. The population of EPOCH was elderly, had multiple comorbidities, and required major emergency intra-abdominal surgery (emergency laparotomy). The post-operative risk of delirium in this population is a potential accelerant of cognitive decline. In addition, the emergency general surgical population makes up 11 percent of surgical cases but 47 percent of surgical deaths. In the UK, all processes of care and outcomes are captured in the UK National Emergency Laparotomy Audit (NELA). To effect systemic change to improve outcomes, EPOCH trial designers had to engage and empower all stakeholders—including patients—and embrace the complexity of existing processes and practices.

EPOCH Trial Design

EPOCH was preceded by a pilot study intended to define evidence-based pathways for patients and then implement quality improvement training. Once EPOCH transitioned out of the pilot phase, it was designed as a stepped-wedge CRT, which involved the sequential transition of clusters (in this case, groups of geographically co-located hospitals) from control to intervention conditions in a randomized order. Ninety hospitals were randomized in 15 geographic clusters with a fixed 85-week intervention period. EPOCH integrated ethnographic and economic analyses, as well as data captured by NELA. With the ability to enroll any eligible patient, the intervention sought to reduce mortality and build an evidence-based pathway to improve care

through training. Local leadership was recruited to champion the training, which was augmented by a national awareness campaign.

The EPOCH study had 90 percent power to detect a reduction in mortality from 25 to 22 percent; although mortality did fall across the study period to 16 percent, no difference between the usual care and quality improvement group was observed. Processes of care did improve in a dose response manner with quality improvement approaches used.

Insights from the EPOCH Study

Delivering the quality improvement program proved much easier than enabling local delivery. Quality improvements leads were often early adopters, which lent credibility to the EPOCH study. Leadership at the chief executive level was also critically important to promoting stakeholder involvement. The social nature of systemic change cannot be understated. To harness the social aspects of systemic change, teams must be able to learn from each other in ways that may be hard to promote in the CRT approach, which was demonstrated in a subsequent collaborative study. The stepped-wedge CRT model was not as useful to participants as it was to the statistical modelers. More dedicated leadership development and assessment of site readiness may be necessary to effectively improve quality.

A follow-on study, The Emergency Laparotomy Collaborative (ELC) applied lessons learned from EPOCH and decreased 30-day mortality from 10.6 percent to 8.7 percent. ELC involved iterative learning processes for providers, such as quality improvement webinars and meetings, virtual site visits, plenary meetings, and awareness campaigns. Insights from these studies have been shared with other groups beyond the UK, including the Improving Care and Surgical Recovery program funded by AHRQ, which include simplifying trials, focusing on a small number of high-impact interventions, and fostering a collaborative atmosphere that leverages stakeholder interest in social change.

Discussion

The stepped-wedge design caused potential bias in EPOCH, particularly the reduced amount of preparation time allotted to participants in the long “tail” of the stepped wedge. As an implementation method, it was not helpful in a context where collaboration is a central component. Compelling reasons should be considered for using a stepped-wedge CRT, and such an approach should be considered carefully if the intervention is complex and must occur over a long period with latter groups having limited time for intervention.

Creating lasting social change requires the involvement of leadership. To entice leaders to consider and invest in policy change, providing data on humane and economic reasons for addressing systemic problems is effective. EPOCH also had the benefit of a national database, which BHCS suggested that NIA should consider.

Diversity, Equity, and Inclusion in Pragmatic Studies to Reduce Health Disparities

Keith Whitfield, Ph.D., President, University of Nevada Las Vegas

Health disparities stem from numerous causes, including differences in insurance coverage, treatment, cultural beliefs concerning health, and the biobehavioral consequences of social inequality. The U.S. economy loses an estimated \$309 billion per year because of the direct and indirect costs of health disparities. Differences in treatment can result in delayed interventions and from an overreliance on emergency departments. Cultural beliefs in minority populations can involve the denial of problems, self-medication, and alternative approaches that are ineffective or cause downstream problems. Biobehavioral consequences arise from the stress associated with racist treatment, poverty, unsafe environments, and poor education—which can act as a proxy measure for limited employment opportunities and social mobility.

Our current understanding of health disparities is limited. We need a better understanding of the mechanisms underlying observed differences. The biobehavioral origins of health disparities must be investigated. Tailoring effective interventions in minority populations requires nuanced understanding of the physical, linguistic, and cultural barriers to care.

Pragmatic Interventions in Minority Populations

Family engagement can facilitate minority recruitment for PCTs. Familial units are a valuable resource and coordination point. Mixed methods approaches are also useful. Iterative approaches that involve both quantitative and qualitative approaches tend to work best. To establish trust with minority populations, PCTs must operate transparently and share insights with participants to avoid the perception of exploitation. Researchers should develop and test hypotheses concerning the underlying mechanisms that create health disparities.

Trial designs may need to oversample minority populations to have sufficient statistical power to detect differences. Strict exclusion policies should be avoided to preserve generalizability. Community liaisons are essential for recruitment. Recruiters should consider regional health disparities, health provider locations, and participants' access to health care, as well as collect information about potential caregivers. Interventions should be directed at health issues that matter to minority populations.

Challenges and Rewards

Significant challenges are inherent in health disparities research. Assessment of changes in health outcomes across generations provides data on how social change affects health. Researchers need to elucidate the causal pathways involved in health and disease to eliminate disadvantages across racial and ethnic groups. Research into health disparities may help clarify the interplay of personal and structural barriers to positive health outcomes. Minority groups may also be able to provide insight into how intersections of social, behavioral, and physical conditions impact interventions. In addition, investigation of health outcomes within family units can expose epigenetic dynamics that contribute to health disparities.

Discussion

More research is needed to understand the high rates of AD/ADRD in Black communities compared to their White counterparts, which may result in part from SDOH, including educational attainment.

For effective AD/ADRD research within minority communities, family involvement is often critical to establish trust and promote study fidelity. One useful recruitment strategy in African American communities is to ask questions and listen to community members to initiate community engagement. Committing upfront to transparent sharing of research insights in exchange for participant involvement is also an effective recruitment strategy. When designing trials, researchers should be mindful of heterogeneity within minority communities and investigate cultural expectations of how community members seek health care. Researchers should also employ diverse recruitment staff to build trust with minority communities, particularly communities experiencing a high burden from oversampling.

Panel Discussion

Catalyzing Transformative Change

Dr. Brody's statements concerning large-scale redesign of systems (i.e., "blowing up the system") led to discussions among presenters and BHCS board members regarding how health care paradigms can be changed to improve primary care for PLWDs and their caregivers. Layered approaches to system redesign are needed, which involves building interdisciplinary care teams of sociologists, psychologists, and social workers—in addition to traditional health care staff. PCTs present a significant opportunity to test these new care models in real-world settings. Integrating care into communities where people live and work is essential. Focusing on preventative care for the highest risk groups before the presentation of moderate and severe outcomes of AD/ADRD may be the most valuable use of resources. Highest risk groups likely include minorities communities and those most subject to stigma.

Industry partners were amenable to transformative change, particularly preventative measures that can stem high downstream costs in AD/ADRD patient populations. To harness the attention and mobilize the involvement of industry stakeholders, clear evidence of the benefit of new care models must be demonstrated. Industry partners were sensitive to equity and diversity issues and understood the potential of multidisciplinary health care teams.

Harnessing social aspects of systemic change is key to gaining widespread stakeholder involvement in new models of primary care. Behavioral economics, including competition and incentivization schemes, are useful to catalyze systemic change. Executive sponsorship and local leadership also offer significant value in ensuring participation in new models of care. New models of primary care should adapt to the current strained conditions in health care. Providing adequate resources for primary care for AD/ADRD patients is daunting, but incorporating novel screening tools (such as giving a small-scale cognition test while taking blood pressure) could efficiently utilize limited resources.

The Challenge of Heterogeneity in PCTs

Accurately measuring intervention effects in PCTs presents analytic challenges. More innovation in PCTs, particularly in developing new methods of interpreting data and study results, could be highly valuable. Understanding the differences in treatment impacts among subpopulations is particularly relevant in AD/ADRD research in minority communities. Understanding how treatment effect may be mediated by intermediate or short-term outcomes is also relevant in AD/ADRD ePCTs and can help identify key constructs in improving the intervention. Moreover, large datasets from completed PCTs should be leveraged and integrated to better understand the context in which AD/ADRD patients reside within their communities and benefit from potential intervention strategies.

Appendix 1. Meeting Agenda

April 3, 2023

8:15	Welcome, Introduction, and Opening Remarks <i>Don Berwick, HCS Board Chair</i>
8:25	Opening Remarks from the Sponsor <i>Theresa Kim, National Institute on Aging</i>
8:40	Evidence for Dementia Care: Tradeoffs Between What We Need and What We Want <i>David Reuben, UCLA David Geffen School of Medicine</i>
9:00	Presentation Questions and Discussion
9:10	Catalyzing Dementia Care Research in Real-World Care Delivery <i>Jennifer Wolff, Johns Hopkins University Bloomberg School of Public Health</i>
9:30	Presentation Questions and Discussion
9:40	Reengineering Care to Meet the Needs of Persons Living with Dementia and Their Care Partners Residing in the Community <i>Ab Brody, NYU Hartford Institute for Geriatric Nursing</i>
10:00	Presentation Questions and Discussion
10:20	Estimand-aligned Considerations in Embedded Pragmatic Clinical Trials <i>Fan Li, Yale University School of Public Health</i>
10:50	Learning about Trial Design and Implementation in a Very Messy World <i>Carol Peden, Blue Cross Blue Shield, University of Southern California, and University of Pennsylvania</i>
11:10	Presentation Questions and Discussion
11:20	Diversity, Equity, and Inclusion in Pragmatic Studies to Reduce Health Disparities <i>Keith Whitfield, University of Nevada, Las Vegas</i>
11:40	Presentation Questions and Discussion
11:50	NIA Session Panel Discussion

Appendix 2. List of Participants

Presenters

David Reuben, UCLA David Geffen School of Medicine
Jennifer Wolff, Johns Hopkins University Bloomberg School of Public Health
Ab Brody, NYU Hartford Institute for Geriatric Nursing
Fan Li, Yale University School of Public Health
Carol Peden, Blue Cross Blue Shield Association, University of Southern California, and
University of Pennsylvania
Keith Whitfield, University of Nevada, Las Vegas

BHCS Members

Donald Berwick, Board Chair
Andrew Bindman, Kaiser Permanente
Niranjan Bose, Gates Foundation
Paul Chung, Kaiser Permanente
Patricia Davidson, University of Wollongong
Martha Daviglus, University of Illinois Chicago
Emily Gee, Center for American Progress
Cindy Gillespie, Arkansas Department of Human Services
Gary Gottlieb, Flare Capital Partners
Elmer Huerta, MedStar Washington Hospital Center
Lauren Hughes, Farley Health Policy Center
Sharon Inouye, Harvard Medical School
Mark Johnson, HighRoads
John Lumpkin, Blue Cross and Blue Shield
Faith Mitchell, Urban Institute
Julie Robison, University of Connecticut Health
William Sage, University of Texas at Austin
Linda Scott, Scott's Solutions
Hardeep Singh, U.S. Department of Veterans Affairs
Laurie Zephyrin, The Commonwealth Fund
Michael Zubkoff, Dartmouth College

National Institute on Aging

Lisbeth Nielsen, Division Director, DBSR
Partha Bhattacharyya, Program Director, DBSR
Jessica Boten, Lead Social Science Analyst, DBSR
Minki Chatterji, Program Officer, DBSR
Melissa Gerald, Program Director, DBSR
Dinesh John, Program Director, DBSR
Theresa Kim, Program Officer, DBSR
Rebecca Krupenevich, AAAS Science & Technology Policy Fellow, DBSR

Emerald Nguyen, Program Official, DBSR
Priscilla Novak, Program Official, DBSR
Lisa Onken, Program Director, DBSR
John Phillips, Branch Chief, BSR
Dana Plude, Deputy Director, DBSR
Elise Rice, Program Director, DBSR
Luke Stoeckel, Program Director, DBSR
Melissa Trevino, Program Director, DBSR

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Kait Lee, Program Analyst
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Jay Weixelbaum, Science Writer